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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Resea
1401 Rockville Pike
Rockville MD 20852-1448

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CBER-98-005

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WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Yasushi Higashi, M.D., D.M.SC
Research Foundation for Microbial Diseases of Osaka
3-1 Yamada-Oka
Suita
Osaka 565, Japan
U.S. License Number 1156

Dear Dr. Higashi:

An inspection of Research Foundation for Microbial Diseases of Osaka facility, located at 2-9-41, Yahata-Cho, Kanonji-City, Kagawa 768, Japan, was conducted from September 15 through September 19, 1997. During the inspection, violations of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act and Title 21, Code of Federal Regulations, Part 211 and Parts 600-610 were documented, as follows:

1. Failure to establish and/or follow written testing programs designed to assess the stability characteristics of drug products including the testing of drug products for reconstitution at the time of dispensing as well as after they are reconstituted [21 CFR 211.166(a)(5)] in that stability testing after reconstitution has been performed on only one lot (EJN**142) of Japanese Encephalitis Virus (JEV).

2. Failure to assure that the equipment used in the manufacture, processing, packing, or holding of a drug product is of appropriate design and of adequate size for its intended use and for its cleaning and maintenance [21 CFR 211.63] in that the Water for Injection (WFI) point of use line #1, which is approximately [redacted] long, represents a dead leg in the system; no procedures exist for draining and flushing the line before use.

3. Failure to establish and/or follow written procedures for cleaning and maintenance of equipment including utensils, used in the manufacture, processing, packing, or holding of a drug product [21 CFR 211.67(b)] in that:

   a. There is no written procedure to specify the locations of air velocity measurements for High Efficiency Particulate Air (HEPA) filters in production areas.

   b. The periodic evaluation of the cleaning method used to clean multi product filling needles and associated silicone tubing for inactivated vaccines is not performed.

   c. There is no written procedure for the sanitization of the Deionized (DI) water distribution system.

4. Failure to clean, maintain, and sanitize equipment and utensils at appropriate intervals to prevent malfunction or contamination that would alter the safety, identity, strength, quality, or purity of the drug product [21 CFR 211.67(a) and 600.11(b)] in that the vent filters for autoclaves and lyophilizers; the filter on the line supplying compressed air to the JEV bulk filtration room ([redacted]); and filters that supply sterile nitrogen to lyophilizers [redacted] and [redacted] during vacuum breaks have not been integrity tested.

5. Failure to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile and to assure that such procedures include validation of any sterilization processes [21 CFR 211.113(b)] in that there is no written procedure to define, explain, and document the simulated manipulations and activities, e.g., mechanical repairs, dislodging jammed vials, employee breaks, and replacement of filling needles, that occur during media fill operations.

6. Failure to maintain separate or defined areas or such control systems as necessary to prevent contamination or mixups [21 CFR 211.42(c)(10) and 600.10(c)] in that the total number of operators permitted in the Class 100 filling area at any one time is not defined as evidenced by records which document between nine to eleven Quality Assurance (QA) and production operators routinely present during filling activities, including media fills.

7. Failure to establish an adequate system for monitoring environmental conditions [21 CFR 211.42(c)(10)(iv)] in that:

   a. Environmental monitoring is not performed during equipment set-up for both product and media aseptic fill operations.

   b. Personnel monitoring procedures only require filling room employees to be monitored on a monthly basis rather than daily basis. In addition, during filling operations which routinely have between nine to eleven employees present in the critical area, all personnel are not monitored, in that the procedures require only two employees be monitored per filling operation.

8. Failure to open, sample, and reseal containers in a manner designed to prevent contamination of their contents and contamination of other components, drug product containers, or closures [21 CFR 211.84(c)(2)] in that the Laminar Air Flow (LAF) cabinets, which are located in Rooms [redacted] and [redacted] and used for sampling raw materials and reagents, are not environmentally monitored.

9. Failure to establish appropriate time limits for the completion of each phase of production to assure the quality of the drug product [21 CFR 211.111] in that time limits have not been established for the sterile bulk filtration and storage of bulk JEV.

10. Failure to routinely calibrate, inspect, or check equipment used in the manufacture, processing, packaging, and holding of a drug product according to a written program designed to assure proper performance [21 CFR 211.68(a)] in that:

    a. The steam sterilization cycles used for the lyophilizers are not revalidated annually in accordance with your written revalidation program.

    b. The thermocouples used to monitor product temperatures during lyophilization cycles are not calibrated.

    c. The temperature of liquid nitrogen storage tanks used for the storage of tissue culture cell lines and working viral seeds used in the production of JEV are not monitored or recorded.

11. Failure to assure that container closure systems provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product [21 CFR 211.94(b) and 600.11(h)] in that integrity testing of the container closure system for JEV vials and bulk Acellular Pertussis Concentrate (APC) has not been performed.

12. Failure to establish laboratory controls that include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity [21 CFR 211.160(b)] in that:

    a. Colony counts are not performed on Biological Indicators which are used for validation and revalidation studies of the autoclaves and lyophilizers.

    b. After sterilization of the rubber stoppers used for final filled vials of JEV, the stopper container is opened in a Class 1000 area for removal of stopper samples for weight measurement; opening the container in a less restricted area could potentially increase the risk of contamination.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deficiencies at your facilities. It is your responsibility as management to assure that your facilities are in compliance with all the provisions of the Federal Food, Drug and Cosmetic Act and all applicable regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts.

Please notify this office in writing, within 15 working days of receipt of this letter, of specific steps you have taken or will take to correct the noted violations and to prevent their recurrence. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions include seizure, license suspension, and/or revocation.

Your reply should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448, Attention: Division of Case Management, HFM-610.

Sincerely,

Cathy Conn

for James C. Simmons
Director, Office of Compliance
Center for Biologics Evaluation and Research